Scientia Pharmaceutica (Sci. Pharm.) **57**, 1–6 (1989)

Degradation of 1-Benzyl-1,2,3,4-tetrahydroisoquinolines (Laudanosine) with Ethyl chloroformate: Gadamer's Intermediate

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(Received May 5, 1988; accepted July 1, 1988)

Gadamer has postulated the α-chlorobisbenzyl derivate **2a** as an intermediate of the degradation of laudanosine [(–)-**1**] to the stilbene **3** by ethyl chloroformate. Optically active **2a** is easily hydrolyzed to the corresponding carbinol **2b**. The optical purity of **2b** is determined via diastereomeric esters.

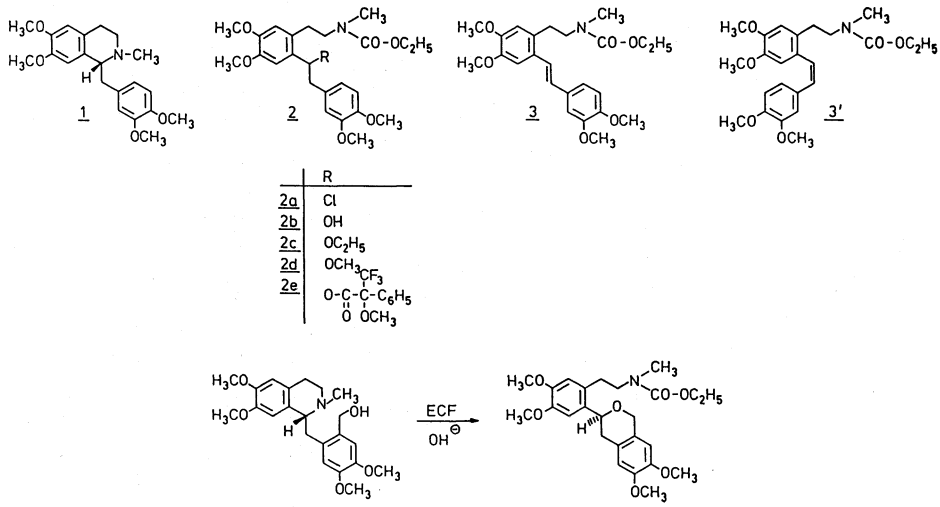
Abbau von 1-Benzyl-1,2,3,4-tetrahydroisochinolinen (Laudanosin) mit Chlorameisensäureethylester: Gadamers Zwischenprodukt

Als Zwischenprodukt des Chlorameisensäureethylester-Abbaus von Laudanosin [(–)-**1**] zum Stilben **3** hat Gadamer das α-Chlorbisbenzylderivat **2a** formuliert. Optisch aktives **2a** wird leicht zum entsprechenden Carbinol **2b** hydrolysiert, dessen optische Reinheit über diastereomere Ester bestimmt wird.

(Keywords: 1-Benzyl-1,2,3,4-tetrahydroisoquinolines, Ethyl chloroformate, Mosher-Esters)

In 1921 Gadamer and Koch[1] reported upon the degradation of (–)-laudanosine [(–)-**1**] to the stilbene **3** with ethyl chloroformate (ECF) in a biphasic system consisting of Et_2O and aqueous KOH. After the reaction, the Et_2O phase was separated

Scheme 1



* Herrn Prof. Dr. Zinner, Braunschweig, zum 65. Geburtstag gewidmet.

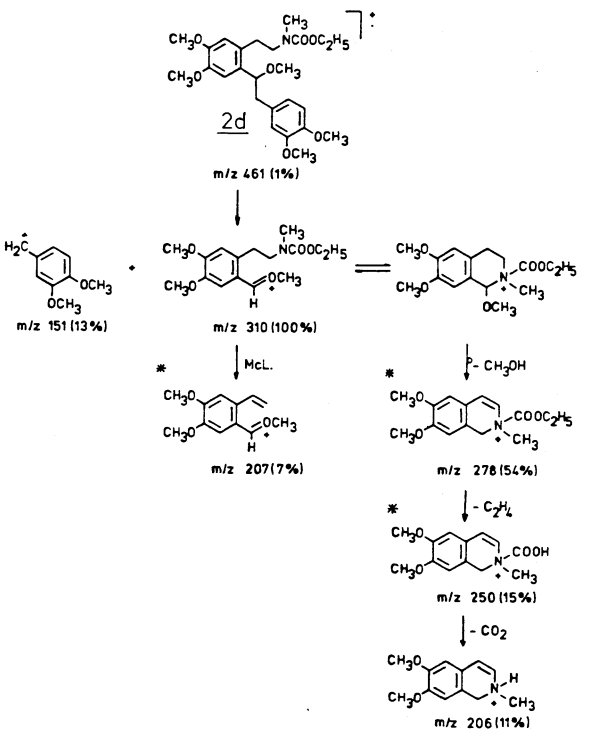
and found to be (+)-rotating. From this Et_2O solution HCl was liberated at room temperature leading to a stilbene „$C_{21}H_{26}NO_4 \cdot CO_2C_2H_5$" identical with the material obtained from racemic laudanosine (**1**). These observations led Gadamer to the assumption of an intermediate which should have structure **2a**[1]. Later on v. Bruchhausen and Knabe[2] found that stilbene **3** has trans configuration, as indicated in formula **3**. In another context we isolated racemic **2a** from racemic laudanosine (**1**)[3].

Our interest in this problems arose when we found that 1-(2'-hydroxymethylbenzyl)-1,2,3,4-tetrahydroisoquinolines (type **A**) are converted to 3-phenylisochromans (type **B**) by ECF. This reaction comprises inversion at C-1 of **A**[4]. So we repeated Gadamer's[1] experiment.

R-(–)-laudanosine [(–)-**1**] was obtained from racemic **1** according to Cava[5] and had 51 % optical purity. **1** was processed with ECF under standard conditions[2, 4]: careful evaporation of the organic layer led to a (+)-rotating crude crystalline material which was separated immediately by HPLC (silica 60; CH_2Cl_2/Et_2O 3 : 2; Fig. 1), indicating 80 % of stilbene **3** besides 18 % of **2a** and 2 % of **2b**, which was identified by comparison with authentic (racemic) **2b**[6]. FD-MS of the crude crystals revealed the molecular ions of **3** (m/z = 429), **2a** (m/z = 465 and m/z = 467), and **2b** (m/z = 447). The chlorourethan **2a** could, however, not be isolated on account of its lability. When we tried to separate **2a** from **3** by column chromatography (CC) (silica; $CHCl_3/Et_2O$) **2a** was converted to **2c** probably by EtOH added to $CHCl_3$ as a stabilizer. This idea was supported by dissolving the crude crystals in MeOH affording the methoxyurethan **2d**.

The MS of **2d** is characteristic for compounds of type **2**.

Scheme 2



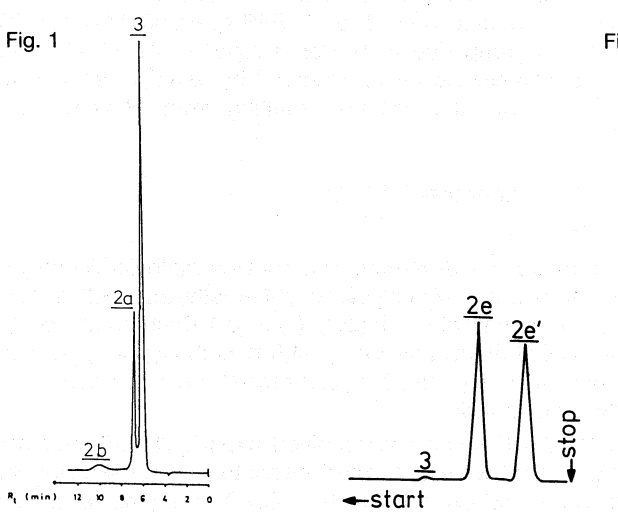
The bisbenzylic bond in $M^{+\cdot}$ is broken producing the ions at m/z = 310 and m/z = 151. Fragmentation processes of the ion at m/z = 310 indicate that it consists of two isomers. McLafferty rearrangement leads to m/z = 207, whilst loss of MeOH is easily explained by assuming a cyclic structure and 1,4-elimination.

The ^{1}H-NMR-spectrum of **2c** reveals two C_2H_5 increments and a triplet for the former H-1 at δ = 4.70 ppm (J = 6 Hz); a triplet of identical chemical shift is reported for the product obtained from laudanosine (**1**) with BrCN/EtOH[7].

2b and **2c** are obtained as optically active materials. A neighbour group effect may explain this observation. The degrees of optical purity and the absolute configurations of **2a**, **2b** and **2c** are unknown, moreover, we can not exclude the possibility that stilbene **3** is formed directly from a quaternary urethan[3].

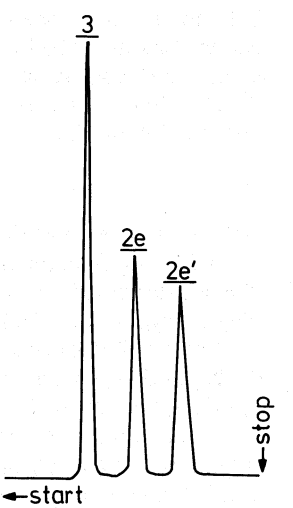
Racemic **2a** had been obtained from **1** as a very labile colourless oil[3]. Optically active **2a** was produced analogously from (–)-**1**. However, our efforts to determine the enantiomer excess (ee) in **2a** failed because it collapses to the stilbene very rapidly. So we converted (–)-**1** into the carbinol **2b** via the intermediacy of **2a** in a one-pot reaction by treatment of (–)-**1** by neat ECF at low temperature (yielding **2a**)[3] and subsequent hydrolysis. We made this experiment because the ee of **2a** must be ⩾ ee **2b** under thermodynamically controlled conditions so permitting a certain conclusion of the optical purity of **2a.** Authentic (+/–)-**2b**[6] could not be resolved by chromatographic methods. Therefore, we transfered it into the corresponding Mosher-esters **2e** (equimolar amount of reagent!) which show separated singlets of the benzylic OCH_3-group (δ = 3.37 and 3.67 ppm) as well as of the N-CH_3-moieties. Moreover, these diastereomers could be separated by HPLC (Fig. 2). With (optically active) **2b** obtained from (–)-**1** (vide supra) the same procedure revealed a ratio 46.5 : 53.5 (Fig. 2a) of the **2b** enantiomers in this experiment. Fortunately this separation is not effected by the stilbene **3** (spiked experiment, Fig. 2b).

Fig. 1



a

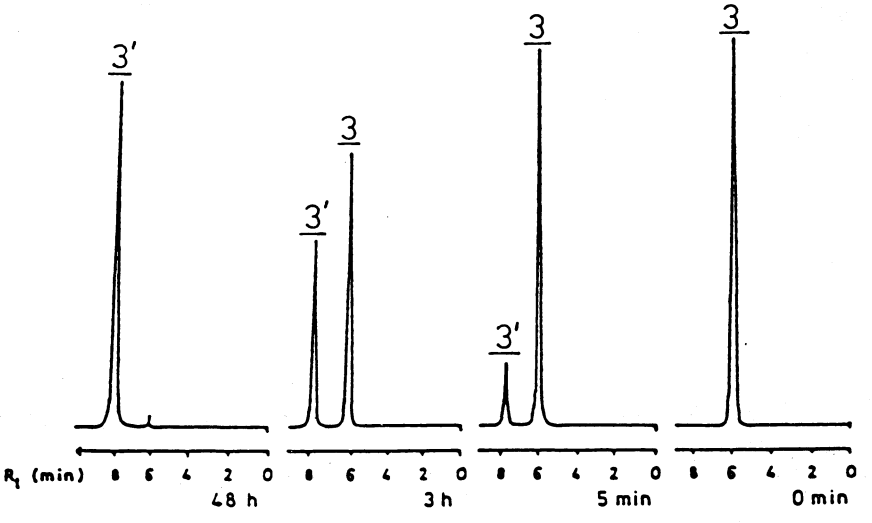
Fig. 2



b

In the context of HPLC separation of Gadamer's reaction mixture (vide supra) we observed a rearrangement of stilbene **3**. **3** being dissolved in MeOH, CH_2Cl_2 or Et_2O, respectively, is converted by diffuse daylight to an oily compound **3'**: When we tried to crystallize **3'** from MeOH **3** was obtained. Without any solvent, however, **3'** crystallized slowly. The conversion of **3** was follwed by HPLC (silica 60; CH_2Cl_2/Et_2O 6:4; Fig. 3).

Fig. 3



Exclusion of light prevents this transformation, pointing towards a trans-cis-isomerization. By scanning of the corresponding peaks the UV spectra of **3** (λ max = 338 nm) and **3'** (λ max = 290 nm) were measured. The ^{1}H-NMR spectrum of **3'** at 0 °C shows two singlets for the N-CH_3-group due to hindered rotation. At 25 °C these signals collapse. A similar photoisomerization was observed by Battersby[8] with 3,3',4,4'-tetramethoxystilbene and with the stilbene resulting from Hofmann-degradation of **1**[8].

Experimental

General remarks and devices: lit.[3,4].

ECF-Degradation of (–)-**1** to trans-2-(β-N-Ethoxycarbonyl-N-methylaminoethyl)-3',4,4',5-tetramethoxystilbene (**3**), 1-[2-(β-N-Ethoxycarbonyl-N-methylaminoethyl)-4,5-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)ethanol (**2b**), (–)-2-(3,4-Dimethoxyphenyl)-1-ethoxy-1-[2-(β-N-ethoxycarbonyl-N-methylaminoethyl)-4,5-dimethoxyphenyl]-ethan ((-)-**2c**) and 2-(3,4-Dimethoxyphenyl)-1-[1-(β-N-ethoxycarbonyl-N-methylaminoethyl)-4,5-dimethoxyphenyl]-1-methoxyethan (**2d**).

(–)-**1** ($[\alpha]_D^{20} = -51°$; [EtOH]) (1.78 g, 5 mmol) was dissolved in $CHCl_3$ (15 ml) and ether (15 ml). 15 % KOH (15 ml) and ECF (3 ml) were added and the mixture was shaken for 2 h. The solution was diluted with water and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and evaporated. The resulting crude crystals had a positive value of rotation.

a) For identification of **2b** (2 %) see Theoretical Part and below.

b) One part of the crude crystals were washed with ether and recrystallized from EtOH to give **3**[1]. The ether solution was evaporated and the resulting crystals were purified by CC (silica: $CHCl_3$/ether 1:1) to give a small quantity of (–)-**2c**: colorless crystals, mp. 69–71 °C. – $[\alpha]_D^{20} = -23°$ (chloroform). – $C_{26}H_{37}NO_7$ (475.6).

IR (KBr): 1695 cm^{-1} (CO).

MS: m/z = 425 (6 %), 324 (100), 310 (19), 278 (65, *238.53), 250 (19, *224.82), 221 (10, *150.74), 206 (19), 204 (35), 151 (35).

UV (MeOH): λ max. (log ϵ) = 234 (4.19), 283 nm (3.81).

^{1}H-NMR: δ (ppm) = 1.18 (t, J = 7 Hz, 3H, $-CH_2-CH_3$), 1.23 (t, J = 7 Hz, 3H, $-CH_2-CH_3$), 2.53–3.93 (m, 8H, $-CH_2-$, $-CH_2-CH_3$), 2.83 (s, 3H, $-NCH_3$), 3.77 (s, 3H, $-OCH_3$), 3.85 (s, 3H, $-OCH_3$), 3.88 (s, 6H, $-OCH_3$), 4.10 (q, J = 7 Hz, 2H, $-CH_2-CH_3$), 4.70 (t, J = 6 Hz, 1H, -O-CH-), 6.58 (s, 1H, Ar), 6.68 (s, 1H, Ar), 6.73 (s, 2H, Ar), 7.03 (s, 1H, Ar).

c) Another part of the crude crystals was stirred with MeOH. The organic layer was evaporated and the product was isolated by preparative HPLC (RP 18; MeOH/water 3:1): **2d**; colorless oil. $C_{25}H_{35}NO_7$ (461.6).

MS: m/z = 461 ($M^{+\cdot}$, 1 %), 310 (100), 278 (54, * 249.30), 250, (15, *224.82), 207 (7), 206 (11), 204 (22), 151 (13).

cis-2-(β-N-Ethoxycarbonyl-N-methylaminoethyl)-3',4,4',5-tetramethoxystilbene (**3'**)

3 was dissolved in MeOH and stirred for 8 d at daylight. The solvent was evaporated: colorless crystals of **3'**, mp. 79–80 °C (crude product).

UV (MeOH): λ max. (log. ϵ) = 290 nm (3.71).

^{1}H-NMR (90 MHz, 0 °C): δ (ppm) = 1.25 (t, J = 7.0 Hz, 3H, $-CH_2-CH_3$), 2.82 and 2.88 (2s, 3H, – NCH_3), 3.10–3.56 (m, 4H, $-CH_2-$), 3.58, 3.66, 3.85, 3.90 (4s, 12H, 4 × $-OCH_3$), 4.11 (q, J = 7.0 Hz, 2H, $-CH_2-CH_3$), 6.56–6.75 (m, 7H, Ar and olefinic H).

(+)-1-[2-(β-N-Ethoxycarbonyl-N-methylaminoethyl)-4,5-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)ethanol [(+)-**2b**]

1.1 g (3 mmol) of (–)-laudanosine [(–)-**1**] (80 % ee[5]) in 20 ml of acetone, 10 ml of water and 1 ml of ECF were stirred for 5 h at room temperature. After evaporation under reduced pressure the $CHCl_3$-extract contains two main products (**3** and **2b**) which were separated by CC (silica; $CHCl_3/Et_2O$ 1:1): 0.5 g (40 %) **2b**, mp. 113.5–114.5 °C, lit.[6]: 112 °C, $[\alpha]_D^{20} = +1°$ (c = 1, MeOH).

$C_{24}H_{33}NO_7$ (447.6)	Calcd.	C 64.4	H 7.43
	Found	C 64.5	H 7.44

IR: 3450 (broad, OH), 1700 cm^{-1} (CO).

MS (70 eV): m/z = 447 ($M^{+\cdot}$, < 1 % (M – H_2O, 52), 326 (429 – $H_3C-N=C(OH)OEt$, McLafferty, 51), 313 (429 – $\cdot H_2C-N(CH_3)-COOEt$, 35), 296 (bisbenzylic cleavage, 94), 222 (100), 193 (296 – $CH_3-N=C(OH)OEt$, McLafferty, 30), 175 (18), 165 (41), 152 (99), 151 (bisbenzylic cleavage, 50), 116 (43).

UV: λ max. (log ϵ) = 279 (3.80) and 202 nm (4.79).

^{1}H-NMR: 1.17 (t, J = 7.5 Hz, 3H, $-CH_2-CH_3$), 2.53–3.60 (m, 3 × $-CH_2-$), 2.83 (s, 3H, $-NCH_3$), 3.78, 3.82, 3.83, 3.87 (4 × s; 12H, 4 × $-OCH_3$), 4.03 (q, J = 7.5 Hz, 2H, $-CH_2-CH_3$), 5.13 (t, J = 6 Hz, 1H, methine-H), 6.53 (s, 1 H, Ar), 6.63–6.83 (m, 3H, Ar), 7.07 (s, 1H, Ar).

Diastereomeric 1-[2-(β-N-Ethoxycarbonyl-N-methylaminoethyl)-4,5-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)ethyl (S)-(–)-[α-methoxy-α-(trifluoromethyl)]phenylacetates (**2e** and **2e'**)

1 g (0.43 mmol) S-(–)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher acid; Aldrich Chem. Co.) was converted to its acid chloride[9]. This chloride was dissolved in 10 ml of CH_2Cl_2 and a few drops of pyridine and reacted with an equimolar amount of optically active **2b** (192 mg) for 3 h at room temperature; the diastereomers of **2e**, which were purified (not separated) by CC (silica; $CHCl_3/Et_2O$ 1:1) were obtained as colorless solid, mp. 126–128 °C, $[\alpha]_D^{20} = -85°$ (c = 1, EtOH).

IR: 1740 (ester), 1695 cm^{-1} (urethan).

FAB-MS: m/z = 663 ($M^{+\cdot}$, 13 %), 512 (12), 430 (100), 429 (31), 384 (21), 327 (71), 313 (32), 278 (49), 222 (16).

UV: λ max. (log ε) = 280 (2.82), 233 (3.27) and 210 nm (3.60).

^{1}H-NMR: δ (ppm) = 1.23 (t, J = 7 Hz, $-CH_2-CH_3$), 2.60–3.60 (m, 7H, 3 × $-CH_2-$ and methine-H), 2.87 and 2.90 (3 × s, 3H, $-NCH_3$), 3.37 and 3.67 (2 × s, 3H, $H_3CO-C^*-CF_3$), 3.77 (s, 3H, $-OCH_3$), 3.87 (s, 3H, $-OCH_3$), 3.90 (s, 6H, 2 × $-OCH_3$), 4.13 (q, J = 7 Hz, 2H, $-CH_2-CH_3$), 6.30–7.47 (m, 10H, Ar).

Separation of **2e***-diastereomers by preparative HPLC*

Phase: Hypersil (Shandon), 300 × 4 mm, room temperature – Eluens: CH_2Cl_2/CH_3CN 95:5, flow: 2 ml/min, pressure: 245 bar. – Manifold: Hewlett-Packard 1084, detection: UV HP, constant wave length.

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